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Andrew P. Feinberg

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EXAMINER

JOHANNSEN, DIANA B

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/629,318	Applicant(s) FEINBERG, ANDREW P.	
	Examiner Diana B. Johannsen	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 August 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,7-18,20 and 21 is/are pending in the application.
- 4a) Of the above claim(s) 21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,4,7-18 and 20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 31, 2010 has been entered. Claims 1, 9, 12 and 17 have been amended and claim 22 has been canceled. Claim 21 remains withdrawn from consideration. Claims 1, 3-4, 7-18 and 20 remain under consideration herein.

Election/Restrictions

2. Claim 21 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 26, 2006.

3. It is again noted that (with regard to claim 9) the elected species of SEQ ID NOS 2-3 is under consideration herein.

Comment regarding claim interpretation

4. It is noted that the recitation in lines 8-9 of claim 1 of "the DMR in the subject" is interpreted as referring back to the DMR "of at least one of the H19 gene and the IGF2 gene" that has previously been subjected to the step of "detecting hypomethylation". Similarly, the recitation in line 6 of claim 10 of "the DMR in the subject" is interpreted as

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referring back to the DMR "of an H19 gene or an IGF2 gene" that has been analyzed with respect to hypomethylation (see lines 2-3).

Claim Rejections - 35 USC § 112, first paragraph

5. Applicant's amendments and arguments are sufficient to overcome the prior rejection of claims 17-18 and 20 under 35 USC 112, first paragraph for lack of written description (specifically, new matter). Applicant cites basis in the specification for the limitation "half-methylation of the normally imprinted gene" with respect to the DMR of IGF2 as recited in claim 17. Accordingly, the new matter rejection of claims 17-18 and 20 has been withdrawn.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3-4, and 7-16 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant amended independent claim 1 and 10 to require that "hypomethylation is as compared to the half-methylation of the normally imprinted gene." While the originally filed specification does disclose hypomethylation as compared to (or relative to) "normal" half-methylation with regard to a DMR of the IGF2 gene (as referenced in the paragraph originally identified by applicant [paragraph 181] in support of the

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amendment and as is additionally referenced/disclosed in, e.g., Tables 3 and 4, as well as paragraphs 168 and 178), the specification does not disclose the concept of "half-methylation of the normally imprinted gene" to the extent that the claims embrace a DMR of the H19 gene, i.e., does not disclose or define a "normally imprinted" H19 gene as being a half-methylated gene. In fact, paragraph 181 provides examples of cases in which imprinting of H19 and methylation of that gene are not related or not clearly related. Further, the specification does not provide any general disclosure of the concept of "normal" imprinting as requiring half methylation. Accordingly, applicant's amendments introduce new matter into the claims.

Applicant's arguments of August 31, 2010 have been thoroughly considered and are persuasive in part, as is reflected in the rejection above. Specifically, upon further consideration, the examiner concurs that the originally filed specification as cited (paragraphs 168, 178, and 181) does support the limitation "hypomethylation compared to the half-methylation of the normally imprinted gene" with respect to the DMR of IGF2 that is embraced by the claims. However, support is lacking with regard to any H19 DMR having half-methylation when "normally" imprinted (and the areas of the specification cited in the remarks do not support such a conclusion with respect to the H19 gene). Accordingly, applicant's arguments are not persuasive with regard to this aspect of the rejection.

8. Claims 1, 3-4, 7-18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods in which hypomethylation of the DMR of SEQ ID NO: 1 in the IGF2 gene (as compared to the half-methylation of this

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DMR in the normally imprinted gene) is detected in human blood or colonic mucosa samples as correlating with LOI of the IGF2 gene in human colorectal cancer (CRC) patients and/or as an indicator of CRC risk in human subjects, does not reasonably provide enablement for methods employing detection of such hypomethylation in a DMR (including a DMR comprising SEQ ID NO: 6) of the H19 gene as compared to half-methylation in “the normally imprinted gene” as indicators of LOI of H19 and/or IGF2, or as indicators of cancer risk (including CRC risk), or for the use of any other types of samples or practice of methods in other types of subjects (i.e., any non-human subjects), or for detection of risk for any other type of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is noted that applicant's amendments and arguments have **overcome** some portions of the prior rejection of record. Specifically, claim 1 now requires that “the biological sample is a blood sample or a colon mucosa sample”. Additionally, upon further consideration, it is noted that the claims are considered enabled with respect to detection of hypomethylation of SEQ ID NO: 1 within the IGF2 gene relative to half methylation of the “normally imprinted” IGF2 gene. However, the claims otherwise remain rejected for the reasons indicated below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the

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invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1-9 are drawn to methods for “identifying loss of imprinting (LOI) of the IGF2 gene in a subject with colorectal cancer” comprising “analyzing a biological sample from the subject for hypomethylation of a differentially methylated region (DMR) of at least one of the H19 gene and the IGF2 gene, wherein the biological sample is a blood sample or a colon mucosa sample,” and “detecting hypomethylation of the DMR in the subject, wherein hypomethylation is as compared to the half-methylation of the normally imprinted gene, and wherein further the DMR of the IGF2 gene comprises SEQ ID NO: 1, wherein detection of hypomethylation of the DMR in the subject correlates with” LOI. Claims 3 and 7-8 further specify that the method comprises analyzing the sample for “hypomethylation of a DMR of the H19 gene comprising SEQ ID NO: 6,” with claim 7 further limiting the DMR to a DMR “comprising a CTCF binding site” wherein the site comprises nucleotides 3010-3172 of SEQ ID NO: 6, and claim 8 further requiring the use a particular primer pair (SEQ ID NOs 23-24). Claim 4 further requires analysis of both a DMR of the H19 gene and a DMR of the IGF2 gene for hypomethylation. Claim 9 requires the use of a particular primer pair in the analysis (of which SEQ ID NOs 2 and 3 have been elected). Thus, claims 1, 3-4, and 7-9 encompass the detection of hypomethylation of a DMR of H19 “wherein

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hypomethylation is as compared to the half-methylation of the normally imprinted gene,” and additionally encompass a “subject” that is any mammalian organism with CRC (see paragraph 68 at page 21).

Claims 10-16 are drawn to methods of "identifying an increased risk of developing cancer in a human subject" comprising "analyzing a biological sample from the subject for hypomethylation of" a DMR of an H19 gene or an IGF2 gene, wherein “hypomethylation is as compared to the half-methylation of the normally imprinted gene, and wherein further the DMR of the IGF2 gene comprises SEQ ID NO: 1,” wherein "detection of hypomethylation of the DMR in the subject correlates with" LOI, and wherein LOI "is indicative of increased risk of the subject developing cancer”. Claim 11 further limits the cancer to CRC. Claim 12 requires the use of the primer pairs SEQ ID NOS 23-24 and SEQ ID NOS 25-26. Claim 13 limits the subject to a subject not known to have a colorectal neoplasm. Claim 14 further specifies that the “H19 DMR” comprises SEQ ID NO: 6. Claim 15 further requires analysis of both a DMR of the H19 gene and a DMR of the IGF2 gene for hypomethylation. Claim 16 further limits the biological sample to a blood sample. Thus, claims 10-16 also encompass the detection of hypomethylation of a DMR of H19 “wherein hypomethylation is as compared to the half-methylation of the normally imprinted gene,” and further (with the exception of claim 11) encompass identifying any type of cancer, and (with the exception of claim 16) encompass the analysis of any type of “biological sample”.

Claims 17-18 and 20 are drawn to a method for “identifying an increased risk of developing cancer in a subject” comprising “analyzing a first genomic DNA sample from

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the subject for hypomethylation of a DMR of an IGF2 gene, wherein hypomethylation is as compared to the half-methylation of the normally imprinted gene, and wherein further the DMR of the IGF2 gene comprises SEQ ID NO: 1, wherein hypomethylation of the IGF2 gene correlates with the loss of imprinting of the IGF2 gene, and wherein a loss of imprinting of the IGF2 gene is indicative of an increased risk of developing cancer, thereby identifying an increased risk of developing cancer in the subject". Claim 18 further limits the cancer to CRC. Claim 20 further comprises "detecting hypomethylation of an H19 DMR comprising SEQ ID NO: 6" (such that claim 17 also clearly embraces such an embodiment). Thus, claims 17-18 and 20 encompass the identification of cancer risk in any type of mammalian subject, and further embrace detection of hypomethylation of a DMR of H19 "wherein hypomethylation is as compared to the half-methylation of the normally imprinted gene," as well as the analysis of genomic DNA obtained from any source from the subject and (with the exception of claim 18) identifying any type of cancer.

It is unpredictable as to whether one of skill in the relevant art could actually use applicant's invention as claimed. The specification provides 2 examples. **Example 1** is described as illustrating "that LOI in normal tissue is associated with either a family history or personal history of colorectal neoplasia" (see page 45). Colon tissue samples and peripheral blood lymphocytes (PBLs) were collected from 421 patients, of which 191 were found to be informative for polymorphisms allowing determination of imprinting status (see page 48, paragraph 163). Imprinting status was determined quantitatively by RT-PCR of RNA (see page 46, par 156), and no significant relationship between LOI

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and age, sex or race was identified (par 164, page 49). The specification states that the “odds of LOI in PBL were 4.4 times greater in patients with a positive family history of CRC compared to their counterparts with a negative family history ($p = 0.003$; Table 1)” (page 49, par 164). The specification also reports that the “odds of LOI in PBL were 4.4 times greater in patients with past or present colorectal neoplasia (adenomatous polyps or cancer) than their counterparts without neoplasia ($p=0.002$; Table 1), indicating a strong association between LOI and colorectal neoplasia” (par 165, page 49). The specification also reports odds 4.7 times greater when patients with a positive family history are excluded ($p=0.01$), as well as stratified odds of LOI that are “4.1 times greater in patients with past or present adenomas but no CRC, compared to patients with no past or present neoplasia ($p=0.016$; Table 1)” and “34.4 fold greater in patients with past or present CRC than in those without colorectal neoplasia ($p<0.0001$; Table 1)”, stating that these latter findings “strongly suggest that LOI is associated with both initiation and progression of colorectal neoplasia” (page 49, par 165 and 166). However, at page 51 (par 167), applicant reports that while all patients with LOI in PBL “also showed LOI in normal colon,” other patients exhibited LOI only in the colon, and that in these patients “no statistically significant association with family or personal history of colorectal neoplasia was found”. Thus, applicant’s above noted findings regarding an association between LOI and initiation and/or progression of CRC pertain to those patients exhibiting LOI in PBL, but not those exhibiting LOI in colon tissues. Rather, it appears in Example 1 that no conclusions with regard to CRC may be drawn based on a finding of LOI in colon tissue samples. The specification also reports

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analysis of the methylation status of DNA at 3 positions in the IGF2 DMR located upstream of exon 3, corresponding to positions 87, 90 and 106 of instant SEQ ID NO: 1 (see page 47). Applicants assayed a total of 24 samples from 12 patients "without known neoplasia", 6 PBL and 6 matched normal colonic mucosa samples having normal imprinting, and 6 PBL and 6 matched normal colonic mucosa samples with LOI (page 51, par 168). The specification reports that the 12 samples with normal imprinting showed a "normal pattern of half-methylation (Fig 1A)" of IGF2, while 11 of the other 12 samples with LOI showed hypomethylation of the IGF2 DMR" with the 12th sample showing abnormal partial methylation of both alleles, referencing Fig. 1B (page 51, par 168). Applicants report that the difference between normal and LOI tissues was significant, with a p value < 0.0001 (page 52, par 168)". With regard to methylation analysis, the specification also teaches that "H19 showed hypomethylation in all cases, regardless of imprinting status," indicating that no association was found between LOI and methylation status of the H19 gene in the assays of example 1. Thus, the data of Example 1 is sufficient to establish an association between a hypomethylation in SEQ ID NO: 1 of the IGF2 gene (relative to half-methylation thereof) and LOI of IGF2 in colon tissues and PBL, as well as an association between CRC in human subjects and LOI of IGF2 in PBLs. **Example 2** is described as illustrating "that loss of imprinting of IGF2 in colorectal cancer is correlated with hypomethylation of the DMR of IGF2, and in at least some colorectal cancer patients with hypomethylation of the DMR of H19" (page 53, par 172). Applicants disclose the use of bisulfite sequencing analysis to determine methylation of the IGF2 DMR sequence as well as CTCF binding site 1 (CBS1) of the

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H19 gene (see page 53, pars 173 and 174) in both knockout cell lines and primary CRCs (see pages 54-57). The specification discloses that both the H19 and IGF2 DMRs were found to be hypomethylated in 3 genetically engineered cell lines exhibiting IGF2 LOI (see par 177 and Table 3). However, the specification provides no evidence that the cell lines examined are, e.g., accepted models of human disease and/or human LOI of IGF2, and does not otherwise establish that the findings in these particular cells are in some way representative of disease mechanisms that occur *in vivo*, nor is such evidence provided by the prior art. The specification further teaches the analysis of 20 primary CRC specimens informative for LOI of IGF2, of which 12 exhibited LOI and 8 exhibited normal imprinting (par 178). The specification reports that all 12 CRCs with LOI exhibited hypomethylation of the IGF2 DMR ($p = 0.000007$) and that all 8 CRCs with normal imprinting showed normal half-methylation of the IGF2 DMR. The specification also states that “We also observed hypomethylation of the H19 DMR in CRC, although the differences were not absolute as in the case of the IGF2 DMR” (par 178, Table 4). An inspection of Table 4 reveals that H19 methylation status at CBS1 and CBS6 in the samples exhibiting LOI of IGF2 is hypomethylated in some cases and (normal) half methylation in other cases, and the specification provides no evidence of a statistically significant association between hypomethylation of any H19 DMR and IGF2 LOI (or CRC or any other cancer). Thus, the data of Example 2 support an association between LOI and hypomethylation of SEQ ID NO: 1 of the IGF2 gene (relative to half-methylation) in primary CRC samples. Accordingly, given the guidance in the specification, one of skill in the relevant art would recognize a correlation between LOI

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of IGF2 and hypomethylation of SEQ ID NO: 1, and would reasonably consider the detection of such hypomethylation/LOI in colonic mucosa and/or PBLs of a human subject as one factor indicating a possible increased risk for CRC in a human subject. With regard to the elected primer pair of SEQ ID NOS 2-3, it is further noted that the specification demonstrates the successful use of this primer pair in the analysis of positions 87, 90, and 106 of SEQ ID NO: 1 for methylation status (see, e.g., page 47 of the specification). However, while the specification also exemplifies the use of primer pairs 23-24 and 25-26 in analyzing H19 gene methylation status (see page 53), the specification does not demonstrate that detection of methylation within this region is relevant to detection of IGF2 gene LOI and/or cancer (as discussed above). Rather, the examples in the specification provide evidence that a total lack of methylation at 3 particular sites in the IGF2 DMR of SEQ ID NO: 1 described above is associated with LOI of the IGF2 gene in human CRC patients, and further that this type of LOI is associated with CRC. Evidence is lacking in the specification with regard to: a) an association between hypomethylation of any locations in the H19 gene and LOI of IGF2 and/or H19, as well as with any type of cancer; and b) successful detection of hypomethylation of the 3 particular sites within SEQ ID NO: 1 of the IGF2 gene as an indicator of LOI and/or cancer in any sample type other than blood or colon tissues. Further, the specification provides no data or evidence indicating that the invention is enabled for use with other cancer types or other types of subjects; applicant exemplifies only the practice of the invention as discussed above in human subjects having a particular type of cancer (colorectal cancer).

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Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance with regard to enablement of a claimed invention. However, in the present case the teachings of the prior art do not provide further enabling guidance with regard to the claimed invention. Regarding claim 1 and claims dependent therefrom, the prior art as exemplified by Cui et al (Nature Medicine 4(11):1276-1280 [Nov 1998]) discloses that LOI of IGF2 was observed in tumor and matched normal colonic mucosa samples in 12 of 27 CRC patients, and in PBL samples of 4 of those patients, whereas 2 of 16 control patients exhibited LOI of IGF2 in normal colonic mucosa, and 2 of 15 patients in PBLs (see entire reference). However, neither Cui et al nor the prior art as a whole establishes hypomethylation of H19 as correlating with LOI of IGF2 in CRC patients, as is required by the claims. Further, Nakagawa et al (PNAS 98(2):591-596 [January 2001]) teach that at least one location with the H19 gene is hypermethylated in CRC patients exhibiting LOI of IGF2 (see entire reference, particularly pages 594-595), indicating that an opposite methylation pattern in H19 is associated with IGF2 LOI and CRC in human patients. With particular regard to claims 10 and 17 and claims dependent therefrom, the closest prior art reference, Ahomadegbe et al (Proceedings of the National Association for Cancer Research Annual Meeting, Vol. 37, p. 598 [April 1996]), discloses the analysis of both LOI and methylation status of IGF2 and H19 genes in two types of invasive breast carcinomas (see entire abstract); however, while Ahomadegbe et al report that both genes are "highly hypomethylated" and that LOI was observed in some samples (6 of 15 inflammatory breast cancers and 1 of 6 non-inflammatory breast cancers), the

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references teaches that the genes were highly hypomethylated "whatever their LOI status." Thus, Ahomadegbe et al do not teach or suggest the existence of a correlation between hypomethylation and LOI in cancer (as is set forth in the present claims). Furthermore, the post-filing date reference of Ito et al (Human Molecular Genetics 17(17):2633-2643 [June 2008]) teaches that further study of IGF2 methylation in association with LOI and various cancers revealed that IGF2 hypomethylation is "highly prevalent" in cancer but is independent of imprinting/LOI (see entire reference, particularly page 2634, right column). It is also particularly noted that Ito et al reference the publication of Cui et al (reference "15") that corresponds to the provisional application of which the present application claims the benefit, and concludes that hypomethylation of DMRO of IGF2 is "not invariably associated" with LOI (page 2636, right column), and further that hypomethylation at this site is also "acquired in peripheral blood with age, but does not predict further risk for breast or colorectal cancer" (see page 2638). Additionally, the post-filing date reference of Jirtle et al (Gastroenterology 126:1190-1201 [April 2004]) teaches that only hypomethylation of DMRO of IGF2 has been found to be "tightly linked with IGF2 loss of imprinting in CRC" (see entire reference, particularly page 1191, bottom of left column). Thus, the teachings of the art as a whole support a conclusion that only a very specific type of hypomethylation related to LOI of IGF2 is associated with human CRC. Finally, with regard to subjects other than non-human subjects, it is noted that the art (like the specification) does not provide evidence of an association between hypomethylation of IGF2 and/or H19 genes and LOI of IGF2 and/or cancer, and that the prior art as exemplified by Jinno et al

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(Human Molecular Genetics 5(8):1155-1161 [1996]) emphasizes the structural differences (rather than any commonalities) between human and mouse H19 loci (see entire reference). Thus, in the present case, the teachings of the prior art do not support further or broader enablement of the invention claimed. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct further experimentation aimed at determining whether applicant's methods may be successfully employed with respect to, e.g., other cancer types, other types of subjects, etc. However, the outcome of such experimentation is entirely unpredictable, and it is unknown as to whether any quantity of experimentation – even an infinite amount – would be sufficient to identify other enabled embodiments embraced by the claims. Such a quantity and type of experimentation is clearly undue. Accordingly, while the specification is enabling with regard to methods in which hypomethylation of the DMR of SEQ ID NO: 1 in the IGF2 gene (as compared to the half-methylation of this DMR in the normally imprinted gene) is detected in human blood or colonic mucosa samples as correlating with LOI of the IGF2 gene in human colorectal cancer (CRC) patients and/or as an indicator of CRC risk in human subjects, it would require undue experimentation to use applicant's invention in a manner commensurate with the instant claims.

With regard to the prior rejection of claims 1, 3-4, 7-18 and 20 for lack of enablement, it is noted that applicant's arguments at pages 11-13 are in fact persuasive with regard to enablement of the claims with respect to the IGF2 DMR of SEQ ID NO: 1 (as was noted above). Upon further consideration, the examiner concurs that the

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Murrell et al reference provides additional evidence that the IGF2 DMR of SEQ ID NO: 1 was found to be hypomethylated in association with CRC, thereby providing an additional line of evidence consistent with the data reported in the specification.

Accordingly, the preponderance of the evidence supports a conclusion of enablement as of the time the invention was made with regard to methods employing detection of hypomethylation in SEQ ID NO: 1 of IGF2 (as compared to half methylation of the normally imprinted gene) in blood or colonic mucosa samples of human subjects as an indicator of IGF2 LOI and/or increased risk of CRC. However, the response does not address the remaining aspects of the rejection, and therefore the rejection has been maintained as set forth above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634